REMARKS

Applicants acknowledge with appreciation the Examiner's rejoining of claim groups I and II. Applicants note that a divisional application has been filed in this case (Application Number 09/478,567, filed 6 January, 2000).

Claims 58, 59, 66, 67, 73-75, 81, 82, 98, 99, 106, 107, and 115 have been amended. Some of these amendments were to correct minor errors of punctuation and spelling and other amendments were to clarify the importance to these claims of nutritionally essential amino acids, per the Examiner's suggestion (Office Action page 4, #9). Accordingly, claims 60, 100 and 116 which depended from claims 58, 98, and 115, respectively, have also been amended to clarify that the amino acids are nutritionally essential.

The Invention

Applicants' invention provides methods for altering amino acid compositions of proteins of interest while at least substantially retaining the native conformation of those proteins. The methods make use of interacting molecules which are capable of binding with the native protein and recognizing its native conformation. These interacting molecules include both antibodies and derivatives thereof as well as non-antibody proteins capable of oligomerization and dimerization with the native protein of interest so long as the object of the invention is achieved, *i.e.*, ascertaining whether the conformation of the protein of interest has been altered by the changes in amino acid composition.

Claim Rejections Under 35 U.S.C. §112, First Paragraph,
Should Be Withdrawn

The Examiner has rejected claims 54-83, 97-107, and 115-118 as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention." (Office Action, page 2). The Examiner goes on to indicate that undue experimentation would be required for those of skill in the art to make and use the invention.

Applicants respectfully disagree with this assessment. The Examiner lists the *Wands* factors for determining whether undue experimentation would be required to practice the invention, and Applicants believe that an assessment of these factors in the present case leads to the conclusion that the disclosure fully enables the invention.

Applicants note that generally the Examiner's enablement rejections are directed toward the embodiments making use of antibodies and further note that many of the Examiner's comments with regard to antibodies are not applicable to oligomerizing or dimerizing proteins. Applicants further note that the use of oligomerizing proteins is provided in the specification (see, for example, page 5) and is also provided in a working example (see the Experimental section at pages 13-23, particularly pages 14 and 21). Thus, the Examiner's objection to claims to the use of dimerizing proteins (for example, claims 57 and 72) should be reversed.

The Examiner supports the enablement rejections by asserting that "the use of antibody binding as a general method to confirm a protein's native conformation is not supported by the prior art." (Office Action, page 3). Applicants respectfully submit that the use of antibody binding as a general method to determine a protein's native conformation is supported by the prior art. For example, Applicants include with this response a copy of the article by Speed *et al.* (1997), *Protein Sci.* 6(1): 99-108, entitled "Conformation of P22 tailspike folding and aggregation intermediates probed by monoclonal antibodies." This article, published about four years ago, illustrates the use of monoclonal antibodies against tailspike chains of P22 bacteriophage to discriminate between completely folded, or native protein, and folding intermediates. Speed *et al.* also discuss (page 99, column 2, second paragraph) that "antibodies have been used to probe the structure of productive folding intermediates formed either *in vitro* or *in vivo*" and describe several examples in which antibodies were used to study protein folding, including the beta-2 subunit of native tryptophan synthase and native bovine serum albumin. As this discussion by Speed *et al.* makes clear, antibodies have been used in many instances to discern between completely folded proteins having their native conformation and proteins which

are only partially folded. This use of antibodies is similar to that of the present invention, which in some embodiments makes use of antibodies to show that the protein retains its native conformation.

Applicants also include with this response a copy of a portion of Friguet *et al.* (1989) "Immunochemical analysis of protein conformation," in *Protein structure/ a practical approach*, ed. Creighton (IRL Press at Oxford University Press, Oxford, England). This chapter (Chapter 12) describes techniques for the production of antibodies suitable for "conformational probes" which may be used to determine a protein's conformation. As is clear from the discussion in this chapter, identification of antibodies suitable for conformational probes involves an amount of work considered in the art to be routine; for example, Friguet *et al.* state, "[o]ften hundreds of hybridoma supernatants are tested" (page 288, last paragraph). Subsection 4 (pages 299-308) is aptly entitled "Antibodies as Conformational Probes." This subsection discusses that "[t]he affinity of an antibody for its antigen depends on the structural complementarily between the two molecules, so changes in the antigen conformation are expected to be reflected in changes in affinity for the appropriate antibodies." This subsection also discusses standard procedures for determining stoichiometry of binding and for measuring affinity of binding. These procedures are readily employed as discussed in subsection 4.4 (page 308) to show that isolated domain portions of a trypsin subunit undergo a conformational change upon assembly. These procedures are representative of those standard in the art which may be used in the practice of the present invention. Because these procedures are standard and well-known in the art, the Examiner's assertions (Office Action, page 3, bottom half of page) that Applicants have not provided sufficient guidance cannot be supported and should be withdrawn.

While it may be true that the practice of the current invention may require more work, or a longer series of steps, than other inventions in other areas of biology, Applicants respectfully disagree with the Examiner's indication that this would amount to undue experimentation or an unduly "large amount of experimentation." The Federal Circuit has long acknowledged that the important consideration in determining whether experimentation is undue or appropriate is what those in the art consider routine. The Federal Circuit has also recognized that immunologically-

based experiments can require more work than experiments in other areas. See, for example, *In re Wands*, 8 USPQ2d 1400, 1406-07 (Fed. Cir. 1988) (noting in 1988, some 13 years ago, that "[t]he nature of monoclonal antibody technology is that it involves screening hybridomas" and "in the monoclonal antibody art it appears that an 'experiment' is not simply the screening of a single hybridoma, but is rather the entire attempt to make a monoclonal antibody against a particular antigen.") As supported by the present disclosure and as further supported by the examples of art included with this response, the amount of experimentation necessary to practice the current invention is considered routine in the art. Accordingly, the Examiner's assertions that undue experimentation would be required to practice the present invention cannot be supported and should be withdrawn.

Thus, as illustrated by the examples of art included with this response, techniques using antibodies to study protein conformation have become routine in the art. Further, there are many techniques known in the art that are routinely used to study interactions between proteins and that could also be used to practice the present invention. For example, Applicants include with this response a copy of the article by Lakey and Raggett (1998) *Current Opinion in Structural Biology* 8: 119-123, "Measuring protein-protein interactions," which describes a number of techniques known in the art and routinely used to study interactions of proteins.

Applicants respectfully submit that for the reasons discussed above, the invention is fully enabled by the present specification and would not require undue experimentation. Accordingly, the rejection under 35 U.S.C. §112, ¶ 1, for lack of enablement should be withdrawn.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

The Examiner has rejected claims 57-60, 66, 67, 73-75, 81, 82, 98-100, 106, 107, 115 and 116 under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner has rejected claim 57, stating that the term "dimerizing proteins" renders this claim indefinite because, *inter alia*, "one of ordinary skill in the art would not be reasonably apprised of the scope of the invention" and "[t]he specification does not teach any dimerizing

proteins." (Office Action, page 4, #7 and #8.) Applicants respectfully disagree. Applicants have provided the use of polypeptides having affinity to the protein of interest to detect conformational changes (see, for example, page 5) and have provided a working example of the use of dimerizing proteins to detect conformational changes (see Experimental section, particularly pages 14 and 21).

Applicants include copies of relevant art with this response to support their position that the notion of oligomerizing and dimerizing proteins is well-known in the art. Applicants include a copy of the definition of "dimer" from *Stedman's Medical Dictionary* (26th edition 1994, William Wood and Company, Baltimore, MD) at page 486, which is "a compound or unit produced by the combination of two like molecules...or by simple noncovalent association." Applicants also include an excerpt from Alberts *et al.*, eds. (1983) *Molecular Biology of the Cell* (Garland Publishing, Inc., New York), which discusses formation of dimers by proteins (page 121). This excerpt states (at page 127) that "[p]roteins are brought together into aggregate structures by the same forces that determine protein folding. Proteins with binding sites for their own surface can assemble into dimers or larger oligomers...." Applicants further include an excerpt from Zubay, ed., (1983) *Biochemistry* (Addison-Wesley Publishing Co., Inc., Reading, MA), page 24, which discusses that multimeric proteins, or oligomers, may be formed from other proteins.

Thus, the notion of oligomerization and dimerization is well-known in the art and one of ordinary skill in the art would be readily able to discern the scope of the invention. Accordingly, the term "dimerizing proteins" does not render the claim indefinite and the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§112, first and second paragraphs, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Version with Markings to Show Changes Made:

58. (Amended) A method for altering amino acid composition of a native protein of interest whose conformation is unavailable, said method comprising introducing amino acid changes into said protein to create an engineered protein, said engineered protein having the conformation of the native protein wherein said conformation of the engineered protein is confirmed by binding said engineered protein with a set of antibodies capable of binding with the native protein, wherein said antibodies recognize native conformation, and wherein said amino acid changes are made to increase levels of nutritionally essential amino acids in the engineered protein.

59. (Amended) The method of Claim 58, wherein said nutritionally essential amino acids are selected from the group consisting of methionine, tryptophan, lysine, valine, phenylalanine, isoleucine, leucine, [theronine] threonine and cysteine.

66. (Amended) The method of Claim 58, wherein said nutritionally essential amino acids are increased to represent 5% of the total amino acid content of the protein.

67. (Amended) The method of Claim 58, wherein said nutritionally essential amino acids are increased to represent 10% of the total amino acid content of the protein.

73. (Amended) The method of Claim 69, wherein said amino acid changes are made to increase levels of nutritionally essential amino acids in the engineered protein.

74. (Amended) The method of Claim 73, wherein said nutritionally essential amino acid is selected from the group consisting of methionine, tryptophan, lysine, valine, phenylalanine, isoleucine, leucine, [theronine] threonine and cysteine.

75. (Amended) The method of Claim 74, wherein said nutritionally essential amino acid

is methionine.

81. (Amended) The method of Claim 73, wherein said nutritionally essential amino acids are increased to represent 5% of the total amino acid content of the protein.

82. (Amended) The method of Claim 73, wherein said nutritionally essential amino acids are increased to represent 10% of the total amino acid content of the protein.

98. (Amended) The method of Claim 97, wherein said amino acid changes are made to increase levels of nutritionally essential amino acids in the engineered protein.

99. (Amended) The method of Claim 98, wherein said nutritionally essential amino acids are selected from the group consisting of methionine, tryptophan, lysine, valine, phenylalanine, isoleucine, leucine, [theronine] threonine and cysteine.

106. (Amended) The method of Claim 98, wherein said nutritionally essential amino acids are increased to represent 5% of the total amino acid content of the engineered protein.

107. (Amended) The method of Claim 98, wherein said nutritionally essential amino acids are increased to represent 10% of the total amino acid content of the engineered protein.

115. (Amended) A method for altering amino acid composition of a native protein of interest, said method comprising introducing amino acid changes into said protein to create an engineered protein having increased level of nutritionally essential amino acids, said engineered protein having the conformation of the native protein wherein said conformation of the engineered protein is confirmed by binding said engineered protein with a set of interacting molecules capable of binding with the native protein, and wherein said molecules recognize native conformation.